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PEDIATRIC RENAL TRANSPLANTATION UNDER TACROLIMUS-BASED IMMUNOSUPPRESSION[1]

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Background. **Tacrolimus has been used as a primary immunosuppressive agent in adult and pediatric renal transplant recipients, with reasonable outcomes.**

Methods. **Between December 14, 1989 and December 31, 1996, 82 pediatric renal transplantations alone were performed under tacrolimus-based immunosuppression without induction anti-lymphocyte antibody therapy. Patients undergoing concomitant or prior liver and/or intestinal transplantation were not included in the analysis. The mean recipient age was 10.6±5.2 years (range: 0.7–17.9). Eighteen (22%) cases were repeat transplantations, and 6 (7%) were in patients with panel-reactive antibody levels over 40%. Thirty-four (41%) cases were with living donors, and 48 (59%) were with cadaveric donors. The mean donor age was 27.3±14.6 years (range: 0.7–50), and the mean cold ischemia time in the cadaveric cases was 26.5±8.8 hr. The mean number of HLA matches and mismatches was 2.8±1.2 and 2.9±1.3; there were five (6%) O-Ag mismatches. The mean follow-up was 4.0±0.2 years.**

Results. **The 1- and 4-year actuarial patient survival was 99% and 94%. The 1- and 4-year actuarial graft survival was 98% and 84%. The mean serum creatinine was 1.1±0.5 mg/dl, and the corresponding calculated creatinine clearance was 88±25 ml/min/1.73 m^2. A total of 66% of successfully transplanted patients were withdrawn from prednisone. In children who were withdrawn from steroids, the mean standard deviation height scores (Z-score) at the time of transplantation and at 1 and 4 years were −2.3±2.0, −1.7±1.0, and +0.36±1.5. Eighty-six percent of successfully transplanted patients were not taking anti-hypertensive medications. The incidence of acute rejection was 44%; between December 1989 and December 1993, it was 63%, and between January 1994 and December 1996, it was 23% (P=0.0003). The incidence of steroid-resistant rejection was 5%. The incidence of delayed graft function was 5%, and 2% of patients required dialysis within 1 week of transplantation. The incidence of cytomegalovirus was 13%; between December 1989 and December 1992, it was 17%, and between January 1993 and December 1996, it was 12%. The incidence of early Epstein-Barr virus-related posttransplant lymphoproliferative disorder (PTLD) was 9%; between December 1989 and December 1992, it was 17%, and between January 1993 and December 1996, it was 4%. All of the early PTLD cases were treated successfully with temporary cessation of immunosuppression and institution of antiviral therapy, without patient or graft loss.**

Conclusions. **These data demonstrate the short- and medium-term efficacy of tacrolimus-based immunosuppression in pediatric renal transplant recipients, with reasonable patient and graft survival, routine achievement of steroid and anti-hypertensive medication withdrawal, gratifying increases in growth, and, with further experience, a decreasing incidence of both rejection and PTLD.**

The efficacy of tacrolimus is a primary immunosuppressive agent in adult renal transplant recipients has been established in a number of single- and multicenter trials (*1–10*). In pediatric renal transplant recipients, however, there is relatively less experience regarding its use as a primary agent (*11–20*). We have previously reported on the use of tacrolimus in pediatric renal transplantation (*11–17*), and have found it to be associated with reasonable patient and graft survival and an ability to withdraw steroids in the majority of successfully transplant patients. This has been associated with improved growth, particularly in preadolescent children. In this report, we present an update of our experience, and discuss strategies to optimize immunosuppression under tacrolimus-based therapy and minimize the incidence of adverse events.

PATIENTS AND METHODS

Between December 14, 1989, and December 31, 1996, 81 pediatric recipients received 82 kidney transplantations only under tacrolimus-based immunosuppression at the Children's Hospital of Pittsburgh (Table 1). Patients undergoing concomitant or previous liver and/or intestinal transplantation were not included in this analysis. The mean recipient age was 10.6±5.2 years (range: 0.7–17.9). Seven (9%) were under 2 years of age, 10 (12%) were between 2 and 5 years, and 65 (79%) were over 5 years of age. Sixty-four (78%) were undergoing their first transplant, and 18 (22%) were undergoing their second (n=11), third (n=5), or fourth (n=2) transplant. Ten of these 18 had received their previous transplants elsewhere. Six (7%) patients had panel-reactive antibody levels over 40%; all were undergoing repeat transplantation. There were 7 (9%) African-American and 75 (93%) Caucasian recipients. The causes of end-stage renal disease are listed in Table 2.

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TABLE 1. Recipient/donor demographics

n=82 (81 patients)	
Recipient age	10.6±5.2 yr (range: 0.7–17.9)
<2 yr	7 (9%)
2–5 yr	10 (12%)
>5 yr	65 (79%)
First transplant	64 (78%)
Repeat transplant	18 (22%)
Second transplant	11 (13%)
Third transplant	5 (6%)
Fourth transplant	2 (2%)
PRA[a] ≥40%	6 (7%)
PRA<40%	76 (93%)
Donor age	27.3±14.6 yr (range: 0.7–50)
Living donor	34 (41%): 31 parents, 1 sister, 1 grandmother, 1 adoptive father
Cadaveric donor	48 (59%)
≤5 yr	9 (19%)
Cold ischemia time	26.5±8.8 hr (range: 9.3–4)
HLA match	2.8±1.2
HLA mismatch	2.9±1.3
0-Ag mismatch	5 (6%)

[a] PRA, panel-reactive antibody.

TABLE 2. Causes of end-stage renal disease

Obstructive uropathy	14 (17%)
Congenital dysplasia	12 (15%)
Membranoproliferative glomerular nephritis	8 (10%)
Focal segmental glomerulosclerosis	7 (9%)
Hemolytic-uremic syndrome	4 (5%)
Polycystic kidney disease	4 (5%)
Prune belly syndrome	3 (4%)
Congenital hypoplasia	3 (4%)
Ureteral reflux	3 (4%)
Chronic glomerulonephritis	2 (2%)
Interstitial nephritis	2 (2%)
Pyelonephritis	2 (2%)
Alport's syndrome	2 (2%)
Cystinosis	2 (2%)
Hereditary nephritis	2 (2%)
Other	9 (11%)
Undetermined	3 (4%)

The mean donor age was 27.3±14.6 years (range: 0.7–50). Forty-eight (59%) cases were with cadaveric donors, 9 (19%) of which were single (n=6) or en bloc (n=3) pediatric donors 5 years of age or younger; the recipients of these pediatric kidneys were all over 10 years of age. The mean cold ischemia time was 26.5±8.8 hr (range 9.3–45.2).

There were 34 (41%) living donors—31 parents, 1 sister, 1 grandmother, and 1 adoptive father.

The mean number of HLA matches and mismatches was 2.8±1.2 and 2.9±1.3, respectively; there were five (6%) 0-antigen mismatch cases.

Immunosuppression was with tacrolimus and steroids, as described previously (*16, 17*). Induction antilymphocyte antibody was not used. Twenty-two percent of patients received azathioprine. Mycophenolate mofetil was not used initially in any patient.

The patient survival rate was calculated from the date of kidney transplantation until death, and the graft survival rate was calculated from the date of kidney transplantation until graft failure, repeat transplantation, or patient death. Survival curves wee generated using the Kaplan-Meier (product limit) method and were compared using the log-rank (Mantel-Cox) test. All tests were two-tailed. A *P*-value less than 0.05 was considered statistically significant.

Until June 1994, when tacrolimus was approved by the U.S. Food and Drug Administration, all transplants were performed under a protocol approved by the Human Rights Committee of the Children's Hospital of Pittsburgh.

The mean follow-up was 4.0±0.2 (SE) years.

RESULTS

The 1- and 4-year actuarial patient survival rates were 99% and 94% (Table 3, Fig. 1). Four patients died, 3–38 months after transplantation, of pancreatitis (3 and 15 months), fungal sepsis (15 months), and unclear etiology, on dialysis (38 months; 18 months after allograft nephrectomy).

The 1- and 4-year actuarial graft survival rates were 98% and 84%. Fourteen patients lost their allografts, 1 week to 58 months after transplantation, to rejection (n=5), recurrent disease (n=5), pancreatitis (n=2), fungal sepsis (n=1), and noncompliance (n=1). Patients undergoing repeat transplantation and sensitized patients with panel-reactive antibody levels over 40% had statistically inferior graft survival rates. Recipients of cadaveric kidneys from donors 5 years of age or younger had graft survival rates similar to those seen in recipients of cadaveric kidneys from donors over 5 years of age.

At most recent follow-up, the mean serum creatinine was 1.1±0.5 mg/dl, and the calculated creatinine clearance was 88±25 ml/min/1.73 m^2. The blood urea nitrogen was 23±8 mg/dl.

The mean tacrolimus dose was 0.18±0.12 mg/kg/day, and the mean level was 9.9±4.6 ng/ml by whole blood IMx. The

TABLE 3. Results[a]

Follow-up		4.0±0.2 yr		
	n	1 yr	4 yr	
Overall actuarial patient survival	81	99%	94%	
Overall actuarial graft survival	82	98%	84%	
First transplant	64	100%	90%	$P<0.02$
Repeat transplant	18	89%	66%	
Cadaveric	48	96%	86%	P=NS
Living donor	34	100%	81%	
PRA <40%	76	99%	87%	$P<0.03$
PRA ≥40%	6	86%	57%	
Recipient <2 yr	7	100%	100%	P=NS
Recipient 2–5 yr	10	90%	60%	
Recipient >5 yr	65	98%	86%	
Cadaveric donor ≤5 yr	9	100%	89%	P=NS
Cadaveric donor >5 yr	39	97%	84%	
Serum creatinine		1.1±0.5 mg/dl		
Calculated creatinine clearance		88±25 ml/min/1.73 m^2		
BUN		23±8 mg/dl		
Off steroids		66%		
Off antihypertensive medications		86%		
Serum cholesterol		155±31 mg/dl		

[a] BUN, blood urea nitrogen; PRA, panel-reactive antibody.

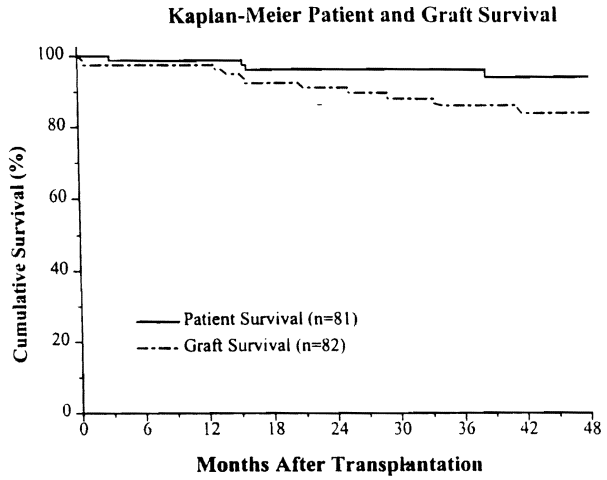

FIGURE 1. Actuarial patient and graft survival.

initial dose was 0.05–0.10 mg/kg/day as a continuous intravenous infusion, followed by a gradual transition to oral tacrolimus 0.15 mg/kg twice daily, with target levels of 20–25 ng/ml for the first 2 weeks, 15–20 ng/ml by 1 month, 10–15 ng/ml by 3 months, and 5–9 ng/ml chronically.

The incidence of delayed graft function was 5%; 2% of patients required dialysis during the first week after transplantation (Table 4).

The incidence of acute rejection and steroid-resistant rejection was 44% and 5%; between December 1989 and December 1993, the incidence of acute rejection was 63%, and between January 1994 and December 1996, it was 23% ($P=0.0003$). This change reflected our success at maintaining the high early target levels (20–25 ng/ml), by gradually reducing the intravenous dosage of tacrolimus while oral tacrolimus was being introduced.

The incidence of cytomegalovirus, either symptomatic disease or asymptomatic infection, was 13% and did not change appreciably over this time period.

The incidence of early Epstein-Barr virus (EBV*)-related posttransplant lymphoproliferative disorder (PTLD) was 9%; between December 1989 and December 1992, it was 17% (5/29 cases), and between January 1993 and December 1996, it was 4% (2/53 cases). All cases were treated with temporary discontinuation of immunosuppression and intravenous gancyclovir, without mortality or short-term graft loss; one patient lost his allograft to chronic rejection 3 years later. In addition, there were two late cases of lymphoma, occurring 3.8 and 4.3 years after transplantation; both patients received chemotherapy with cyclophosphamide, vincristine, methotrexate, adriamycin, etoposide, cytosine arabinoside, and prednisone (one patient also required central nervous system radiation), with complete eradication of the lymphomas in both cases. Both patients were restarted on low-dose tacrolimus 5 months after completion of chemotherapy, and both have maintained allograft function 7.2 and 6.4 years after transplantation.

Insulin-dependent posttransplant diabetes mellitus (PTDM) was seen initially in 9% of successfully transplanted patients. After reduction of tacrolimus and steroid dosing, the final incidence was 1%.

At most recent follow-up, 66% of successfully transplanted patients were off steroids (Table 3). The mean steroid dose was 0.04±0.09 mg/kg/day; in the patients still taking prednisone, it was 0.17±0.11 mg/kg/day. Standard deviation scores (Z-scores) at the time of transplantation and at 1 and 4 years after transplantation were −2.3±2.0, −1.7±1.1, and +0.08±2.5 for all patients, and −2.3±2.0, −1.7±1.0, and +0.36±1.5 in patients taken off prednisone (Table 5). Eight-six percent of patients were off antihypertensive medications, and the mean serum cholesterol level was 155±31 mg/dl (Table 3).

DISCUSSION

This report extends our previous work demonstrating the efficacy of tacrolimus as a primary immunosuppressive agent in pediatric kidney transplantation. Reasonable 1- and 4-year actuarial patient and graft survival rates of 99% and 94%, and 98% and 84%, respectively, have been achieved. Two-thirds of the successfully transplanted recipients were able to discontinue steroids, and in many cases achieved normal growth. Eighty-six percent of the patients were able to discontinue antihypertensive medications, and the mean serum cholesterol level was normal. The incidence of delayed graft function was low, and, with increasing experience, the incidence of acute rejection has fallen to 23%, with a very low rate of steroid-resistant rejection. Maintaining high tacrolimus levels during the first 2 weeks has played an important role in decreasing the rate of acute rejection.

In spite of these favorable outcomes, there have been very

* Abbreviations: EBV, Epstein-Barr virus; PTDM, posttransplant diabetes mellitus; PTLD, posttransplant lymphoproliferative disorder.

TABLE 4. Adverse events

Delayed graft function	5%
Dialysis in first week	2%
Rejection	44%
12/89–12/93	63%
1/94–12/96	23% ($P=0.0003$)
Steroid-resistant rejection	5%
Cytomegalovirus	13%
Early PTLD	9%
12/89–12/92	17%
1/93–12/96	4%
Late lymphoma	2.4%
PTDM	
Initial	9%
Final	1%

TABLE 5. Standard deviation scores (Z-scores)

Time of transplantation		−2.3±2.0
1 yr		−1.7±1.1
4 yr		+0.08±2.5
	Off steroids	On steroids
Time of transplantation	−2.3±2.0	
1 yr	−1.7±1.0	−2.0±1.1
4 yr	+0.36±1.5	−0.6±2.9
	≤12 yr	>12 yr
Time of transplantation	−2.3±2.2	−2.2±1.7
1 yr	−1.5±1.0	−1.9±1.3
4 yr	−0.84±3.0	−1.6±1.3

few published reports from other centers regarding the use of tacrolimus as a primary immunosuppressive agent in pediatric kidney recipients. There have been two reports, from the University of Minnesota (*18*) and Johns Hopkins (*19*), with excellent short-term patient and graft survival statistics, and one abstract from Hannover (*20*) describing less favorable outcomes in three repeat transplant recipients who had developed recurrent hemolytic uremic syndrome under cyclosporine with their first transplants. This paucity of reports from other centers is probably related to the early high incidence of viral complications, especially PTLD, reported by our program (*13*, *15*, *16*), and, to a lesser extent, the incidence of PTDM (*21*). It is worth noting that the observed incidence of early PTLD has declined markedly, as more experience has been gained with tacrolimus. There are several reasons that have contributed to this reduced incidence. The first has been an aggressive policy of tapering both tacrolimus and steroids, with the goal of discontinuing steroids and maintaining low chronic trough levels of 5–9 ng/ml (*16*, *17*). The second has involved prophylaxis, in the EBV-seropositive donor/EBV-seronegative recipient, with gancyclovir and cytomegalovirus hyperimmune globulin, both of which are known to have a significant anti-EBV activity (*22*, *23*). The third has been, in recent years, improved monitoring using EBV serology and polymerase chain reaction testing, to detect primary EBV infections before they become PTLD (*24*). Finally, once patients have been tapered to a stable tacrolimus dose, it is generally unnecessary to raise the dose; children do not outgrow their tacrolimus requirement. Thus, it should be possible to reduce to a minimum the incidence of PTLD.

Tacrolimus-induced PTDM is another important adverse event, but is readily reversible with gradual dosage reduction of tacrolimus and tapering or even discontinuing prednisone (*25*, *26*). Virtually all cases of PTDM in the pediatric patients have been transient.

The other two important side effects of tacrolimus, nephrotoxicity and neurotoxicity, have been well described and are generally reversible with dosage reduction (*27–32*). They are not different qualitatively or quantitatively from those described with cyclosporine-based regimens.

The attainment of normal growth has been an important, but not always achievable goal of pediatric renal transplantation. The only group of pediatric patients who have come close to this goal are those who have been able to discontinue steroids, and tacrolimus is the first agent that can allow routine steroid withdrawal.

There are significant potential benefits associated with tacrolimus-based immunosuppression in children, and, with increasing experience, the incidence of adverse events, such as rejection and PTLD, can be reduced. The expanded use of tacrolimus in pediatric kidney transplantation should, therefore, be given serious consideration by the pediatric nephrology and transplant community.

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A NEW ALLOCATION PLAN FOR RENAL TRANSPLANTATION[1]

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United Network for Organ Sharing Region 1 Renal Data Committee

Background. **A novel plan of renal allograft allocation has been conducted by United Network for Organ Sharing Region 1 transplant centers since September 3, 1996, based upon HLA matching, time waiting, and population distance points. The objectives of this plan were to achieve a balance between increasing the opportunity of renal transplantation for those patients listed with long waiting times and promoting local organ donor availability.**

Methods. **A single list of candidates was formulated for each cadaver donor, assigning a maximum of 8 points for time waiting, a maximum of 8 points for population distance from the donor hospital, and HLA points based upon the degree of B/DR mismatch. Additional points were awarded to a cross-match-negative patient with a panel-reactive antibody of >80%, and to pediatric patients.**

Results. **The total number of kidneys transplanted to patients who had waited >3 years was 100 (46%), and to patients who had waited >2.5–3 years was 29 (13%). However, the total number of kidneys transplanted to patients with the maximum population distance points was only 72 (33%). Thus, although the plan achieved a favorable distribution of kidneys to patients with longer waiting times (nearly 60%), the other, equally important objective of promoting local donor availability was not initially accomplished. Moreover, minor HLA B/DR differences between the donor and the recipient (i.e., not phenotypically matched) were unexpectedly consequential in determining allocation.**

As a result of these observations, the following adjustments were made in the plan (as of December 3, 1997): a maximum of 10 points for population distance, a maxi-

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